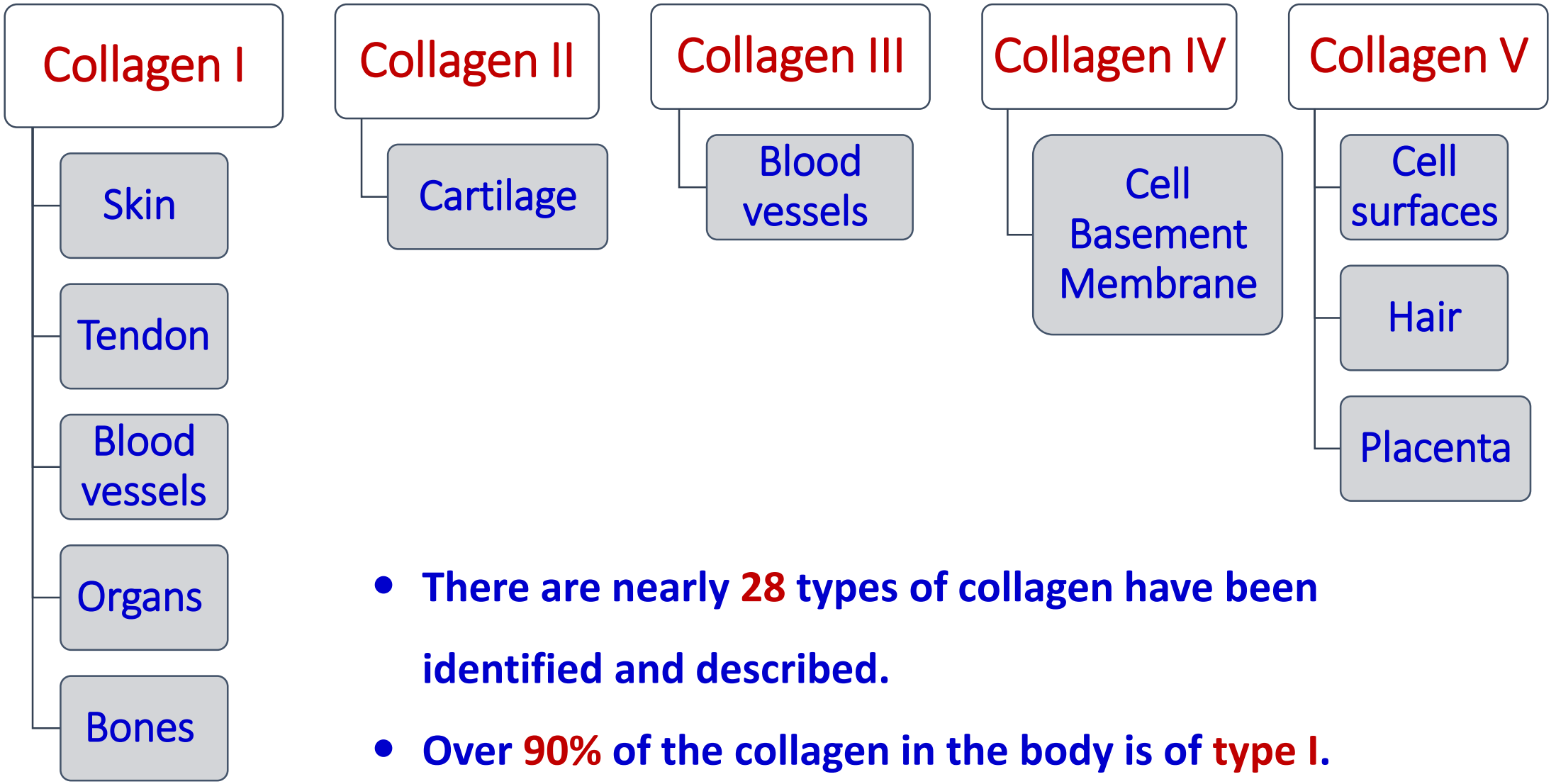
Collagen & Collagen Disorders

Collagen

- Collagen is the most abundant protein in human body (25% to 35%) of the total body protein.
- Collagen is the predominant extracellular matrix protein.
- Collagen is the main fibrous structural component of skin, bone, tendon, cartilage and dentin.

Collagen Functions in Different Organs

1. Collagen dispersed as gel in vitreous humor of the eye.
2. Cornea of the eye → collagen is stacked, so as to transmit light with minimum of scattering.
3. Bundled in tight fibers in tendons.
4. Bones → collagen occurs as fibers arranged at an angle to each other, so as to resist mechanical shear from any direction.



- **There are nearly 28 types of collagen have been identified and described.**
- **Over 90% of the collagen in the body is of type I.**
- **The five most common types are:**

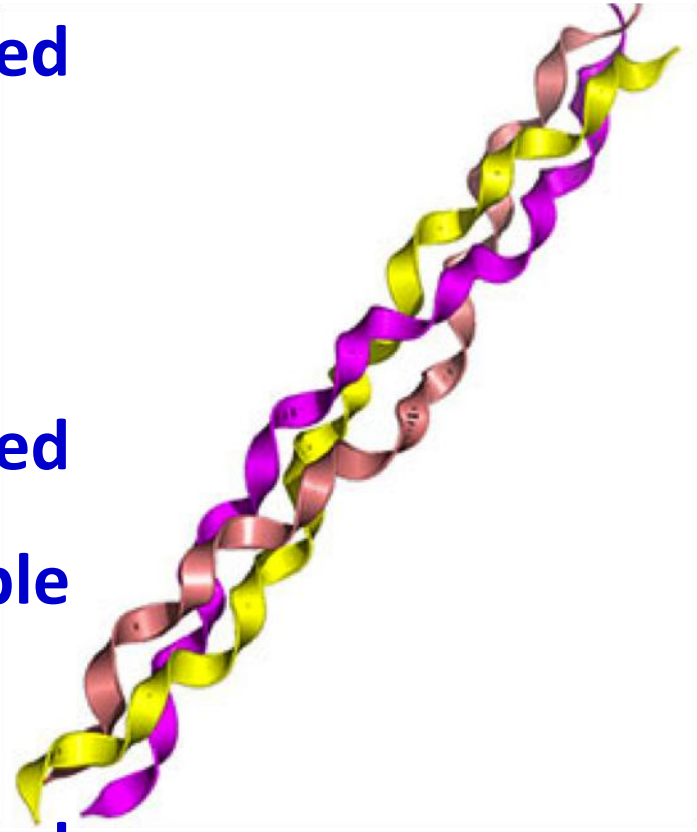
Type	Tissue Distribution
	Fibril-forming
I	Skin, bone, tendon, blood vessels, cornea
II	Cartilage, Inter-vertebral disk, vitreous body
III	Blood vessels, fetal skin
	Network-forming
IV	Basement membrane
VII	beneath stratified squamous epithelia
	Fibril-associated
IX	Cartilage
XII	Tendon, ligaments

Functions of Collagen

1- It imparts strength, support, shape and elasicity to the tissues.
   - ❖ It accounts for 6% of the weight of strong, tendinous muscles
2- It provides flexibility, support, and movement to cartilage.
3- It encases and protects delicate organs like kidneys and spleen.
4- It fills the sclera of the eye in crystalline form.
5- Teeth(dentin) are made by adding mineral crystals to collagen.
6- Collagen contributes to proper alignment of cells for cell proliferation and differentiation.
7- When exposed in damaged blood vessels, it initiates thrombus formation

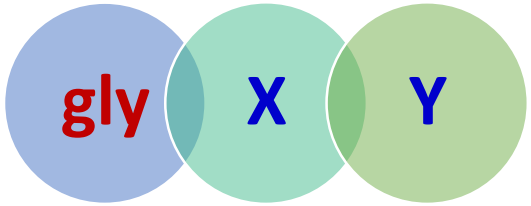
Triple Helix Structure of Collagen

- Collagen is formed of three polypeptide chains, called alpha chains.
- Alpha chains have a conformation of a left-handed helix.
- Further, the three left-handed helices are twisted together into a right-handed coiled forming a triple helix or "super helix".
- The final cooperative quaternary structure is stabilized by numerous hydrogen bonds.



Arrangement of Amino Acids in Collagen

- Collagen is a protein made up of repeating sequence of α-amino-acids.
- The sequence often follows the pattern:
- where X →frequently Proline
- Y → hydroxyproline or hydroxylysine.
- Hydroxy gp of hydroxylysine enzymatically glycosylated with glucose or galactose.
- Collagen rich in Proline and Glycine is important in the formation of the standard triple helix.
- Hydroxyproline is important in stabilizing the triple helical str. and maximizes interchain hydrogen bonds formation.
- Collagens do not contain chemically reactive side groups.



AMINO ACID SEQUENCE (STRUCTURE CONTINUED)

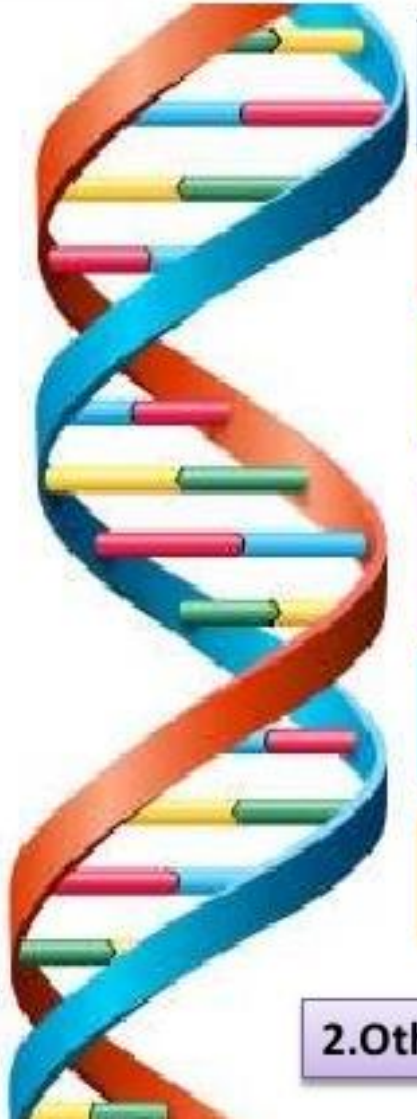
•Collagen is rich in PROLINE,HYDROXYPROLINE& GLYCINE

PROLINE : Helps in the formation of helical orientation of each α chain

GLYCINE : The smallest amino acid found in every 3rd position in the polypeptide chain

BIOSYNTHESIS OF COLLAGEN

Sites For The Synthesis of Collagen :



1.Mesenchymal Cells & Their Derivatives

FIBROBLASTS (major cells)

Chondrocytes

Osteoblasts

Odontoblasts

CEMENTOBLASTS

2.Other Cells : Epithelial cells. Endothelial cells. Muscle cells. Schwann cells.

SYNTHESIS OF COLLAGEN

Gene Expression

(Nucleus)

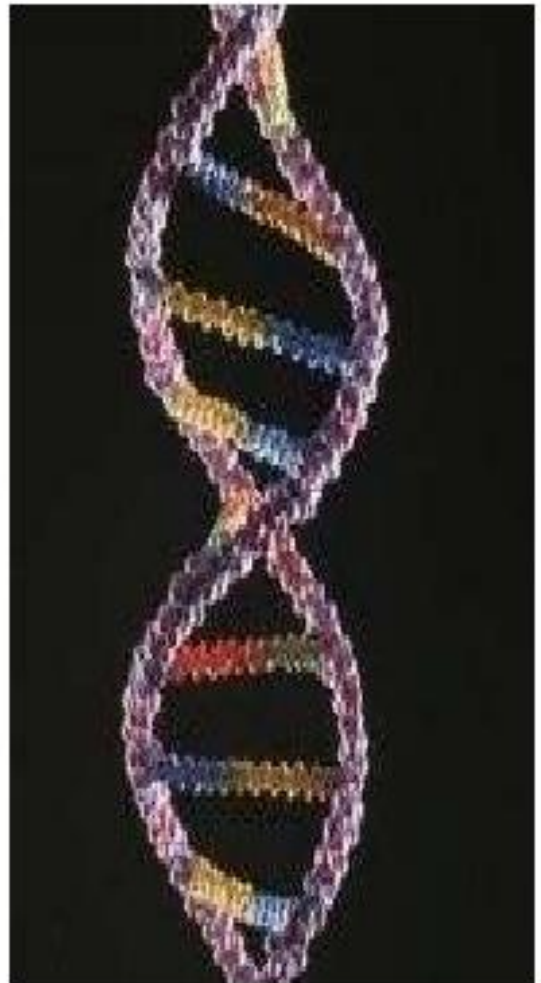
Translational and post translational events or intracellular steps in collagen synthesis procollagen formation .

(Cytoplasm)

Extracellular collagen biosynthetic events

(Extracellular)

Regulation of Synthesis



Formation of Type I collagen

A. Within the cell:

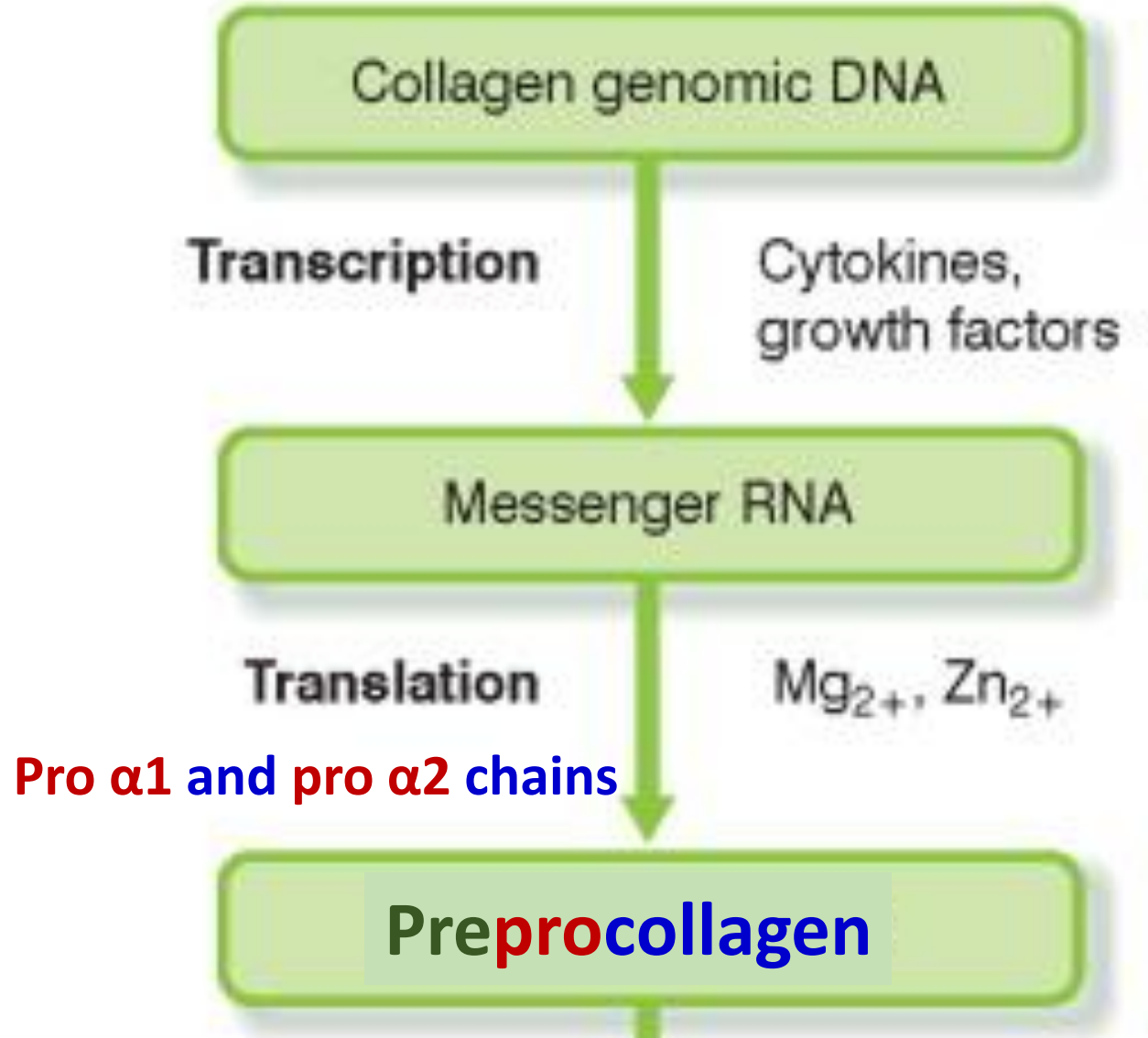
1. In the nucleus: DNA → mRNA.

- Genes for pro α1 and pro α2 chains are transcribed into mRNA.

2. In the ribosomes: During translation, two types of peptide chains are formed on ribosomes along the rough endoplasmic reticulum (RER), (α1 and α2 chains or named preprocollagen).

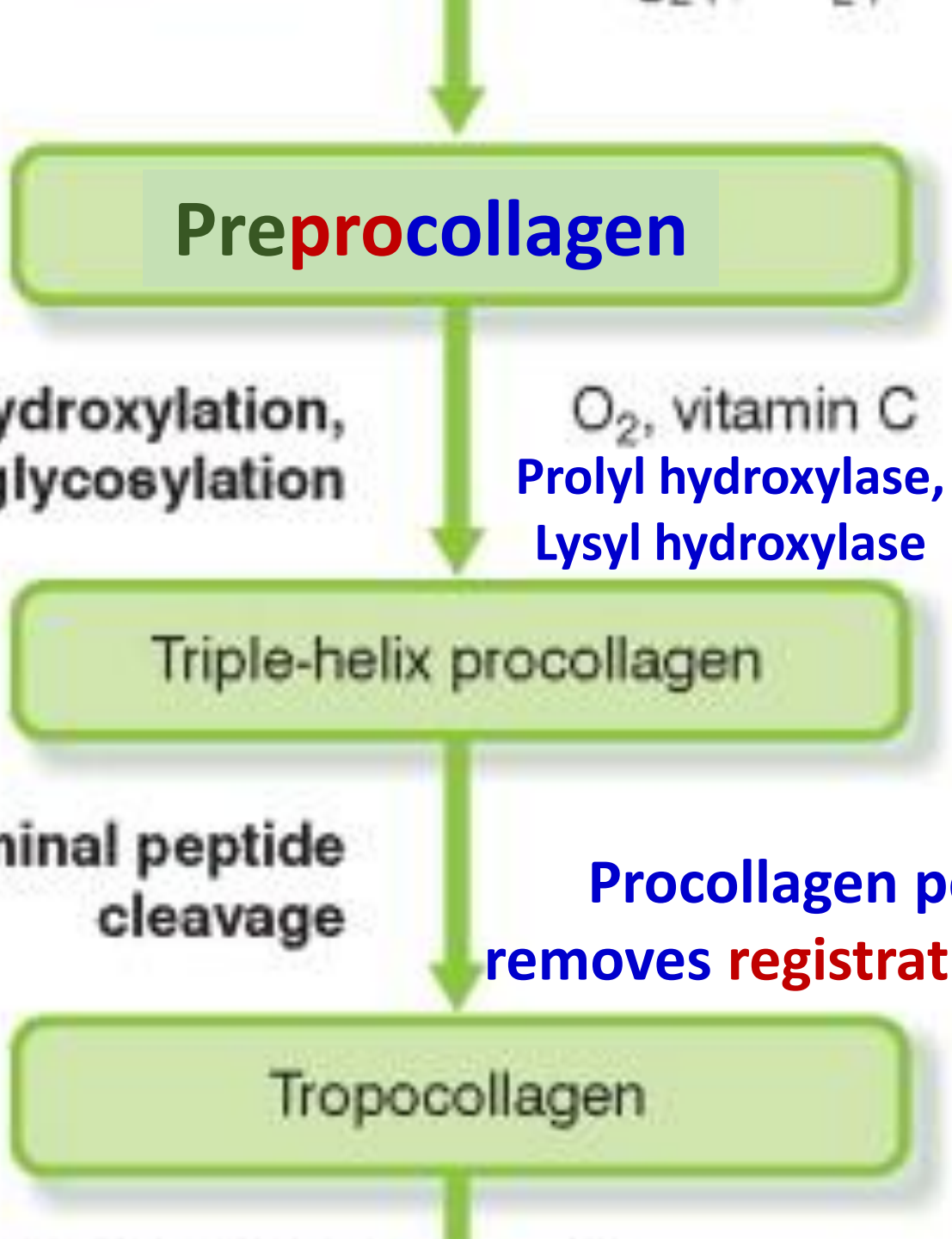
- Each peptide has a registration peptide on each end and a signal peptide.

Collagen synthesis and regulation in wound healing



Formation of Type I collagen

3. The preprocollagen is then released into the lumen of the RER, where signal peptide is removed and the peptide chains are now called pro α-chains .
4. Hydroxylation of lysine and proline occurs inside the lumen of RER. This process is dependent on L-ascorbic acid (Vitamin C) as a cofactor.
5. Glycosylation of specific hydroxylysine residues occurs.
6. After hydroxylation and glycosylation , 3 pro α-chains assemble and form triple helical structure inside the endoplasmic reticulum, this is called procollagen.
7. Procollagen is transported into the Golgi apparatus, where it is packaged and secreted by exocytosis.



In Endoplasmic Reticulum

(3 pro α-chains)

In Golgi apparatus

Procollagen peptidase removes registration peptides

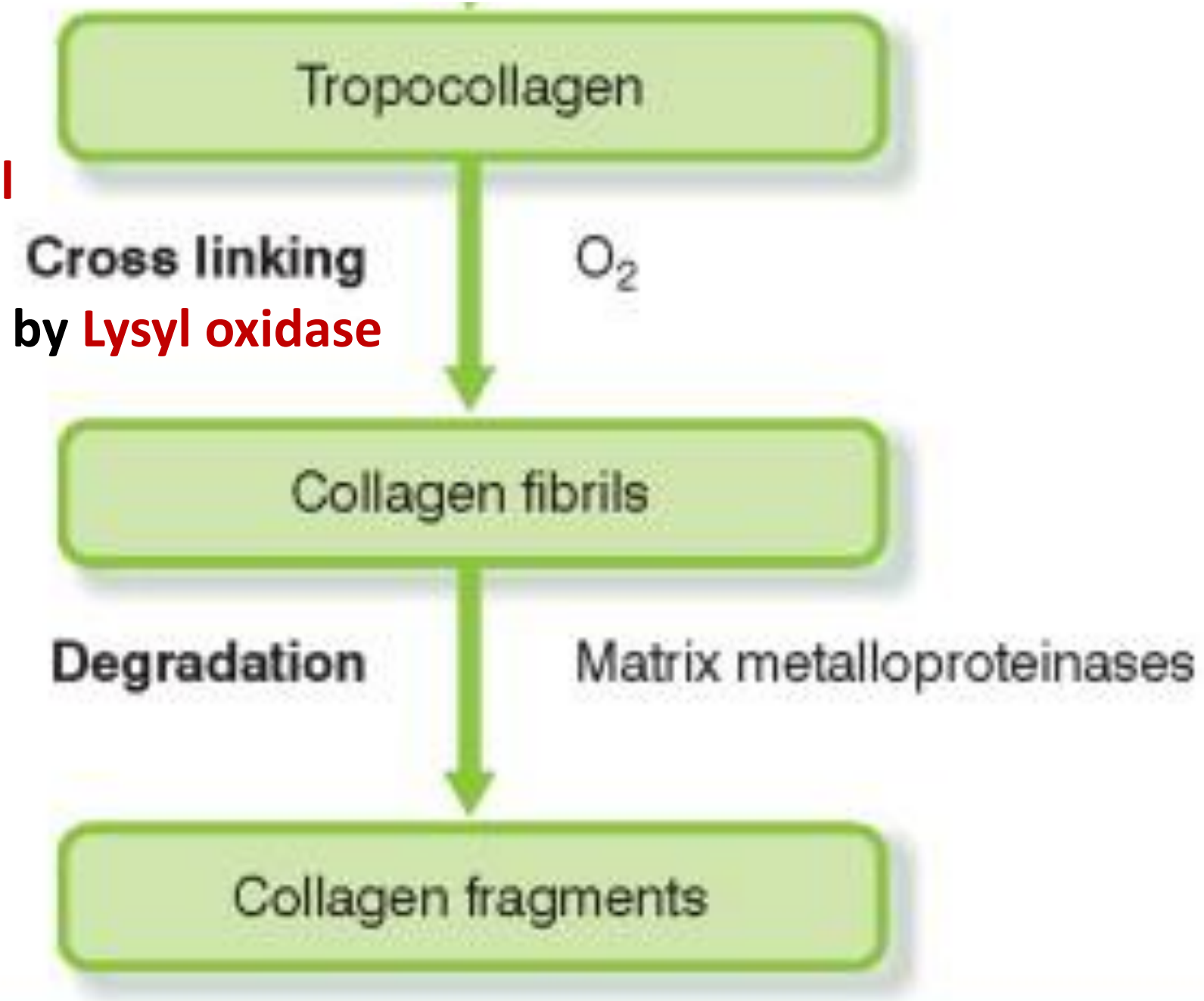
Outside the cell

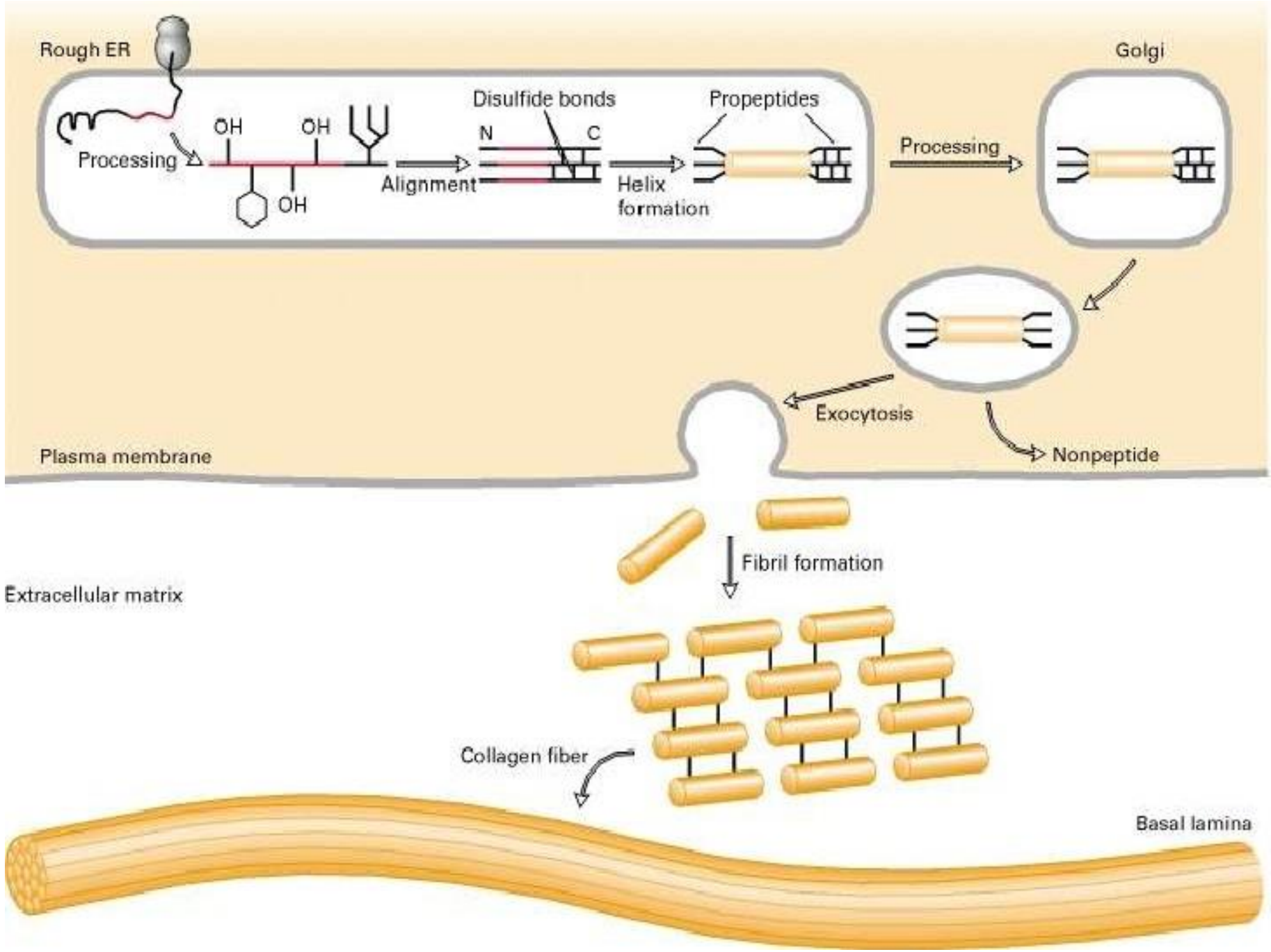
Formation of Type I collagen

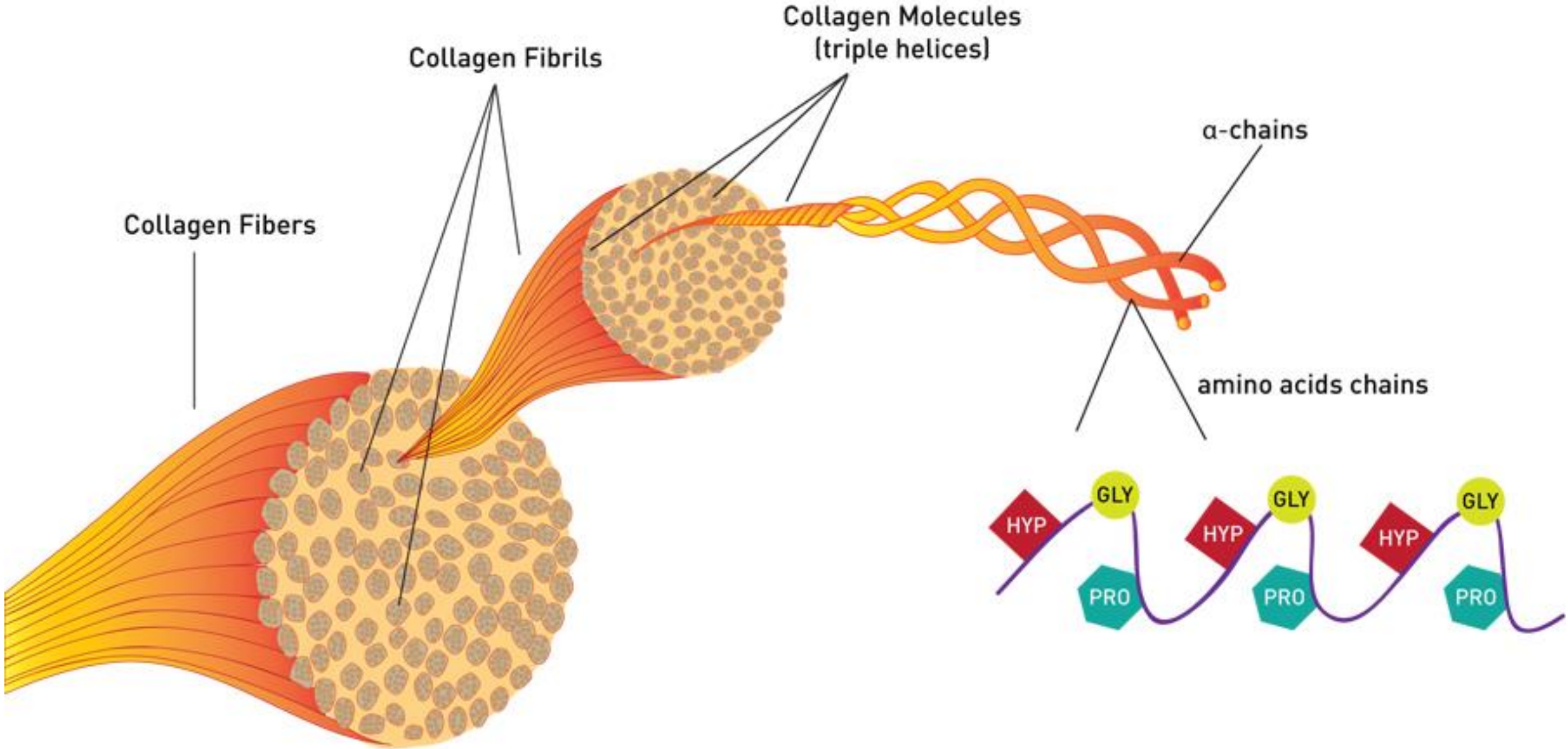
B. Outside the cell:

1. The registration peptides are cleaved by procollagen peptidase and tropocollagen is formed.
2. These tropocollagen molecules gather to form collagen fibrils, via covalent cross-linking by lysyl oxidase which links hydroxylysine and lysine residues.
3. Multiple collagen fibrils form into collagen fibers.

Outside the cell




Rough ER
Golgi
Disulfide bonds
Propeptides
N
C
OH
OH
OH
Processing
Alignment
Helix formation
Processing
Exocytosis
Nonpeptide
Plasma membrane
Extracellular matrix
Fibril formation
Collagen fiber
Basal lamina


Collagen Molecules
(triple helices)
Collagen Fibrils
α-chains
Collagen Fibers
amino acids chains
HYP
GLY
PRO
HYP
GLY
PRO
HYP
GLY
PRO

COLLAGEN DEGRADATION

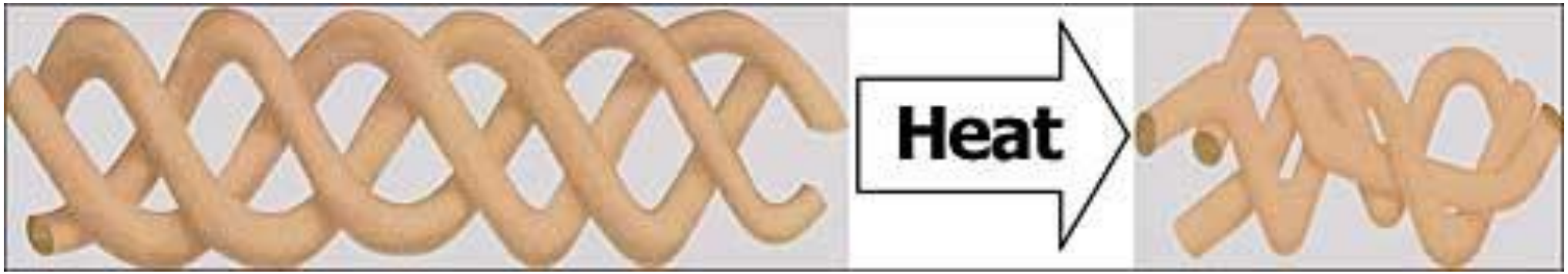
Degradation of Collagen

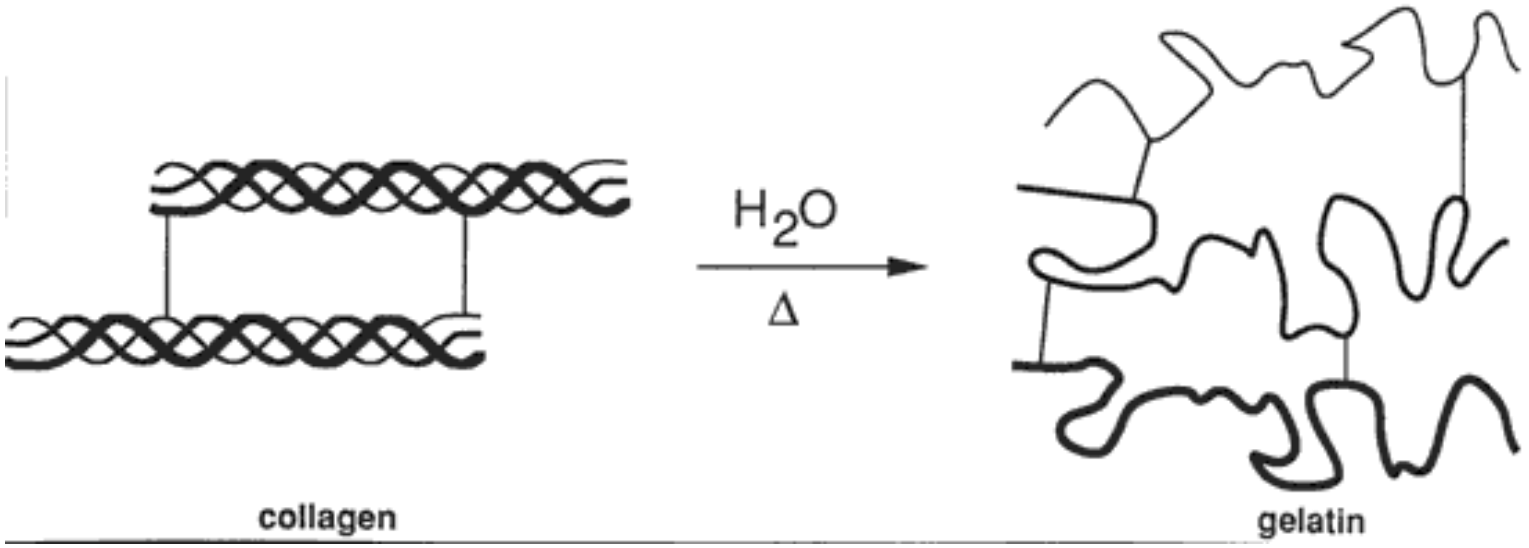
- - - - - -(EQUILIBRIUM BETWEEN DEGRADATION & SYNTHESIS)- - - -

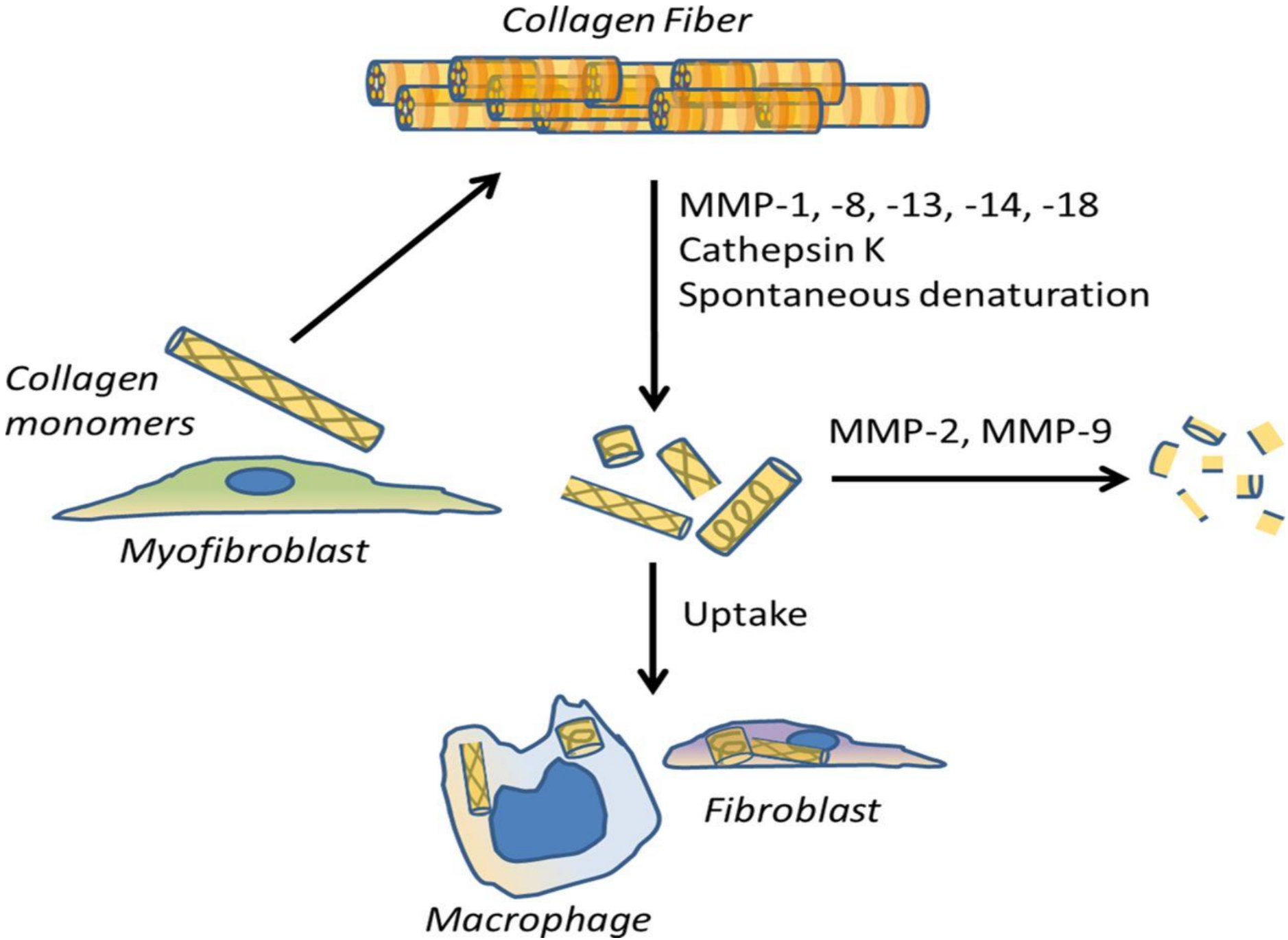
Degradation/Denaturation of Collagen

- Normal collagens are highly stable molecules having half-lives as long as several years.
- Breakdown of collagen fibers depend on proteolytic action of collagenases.
- For type I the cleavage site is specific generating different length fragments which degraded by other matrix proteinases to their constituent amino acid.

Degradation/Denaturation of Collagen






Collagen Fiber
MMP-1, -8, -13, -14, -18
Cathepsin K
Spontaneous denaturation
Collagen
monomers
Myofibroblast
MMP-2, MMP-9
Uptake
Fibroblast
Macrophage

Increased collagenase activity

a. acute inflammation
b. immune mediated cell injury
c. mast cell degranulation
d. bacterial infection
e. tumor invasion

Decreased collagenase activity

a. cirrhosis
b. scleroderma
c. osteopetrosis

Collagen Diseases (Collagenopathies)

- Defects in any one of steps in collagen fiber synthesis result in genetic disease involving inability of collagen to form fibers which provide tissues with tensile strength.

1. Osteogenesis Imperfecta

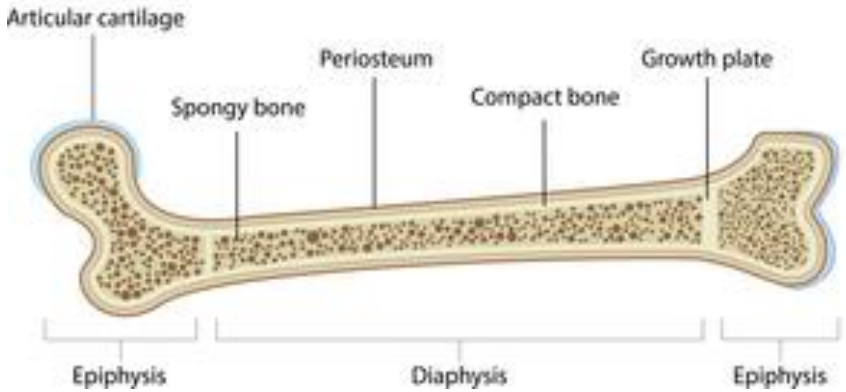
(Brittle Bone Disease)

- **The disease is characterized by:**

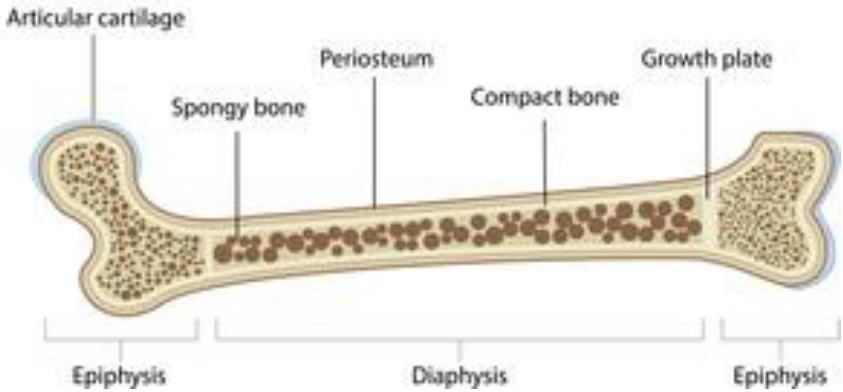
1. **Extremely fragile bones:**
   a) **Reduced bone mass.**
   b) **Degenerated organization of bone tissue.**
   c) **Altered bone geometry in size and shape.**
2. **Irregular connective tissue.**
3. **Blue sclera.**

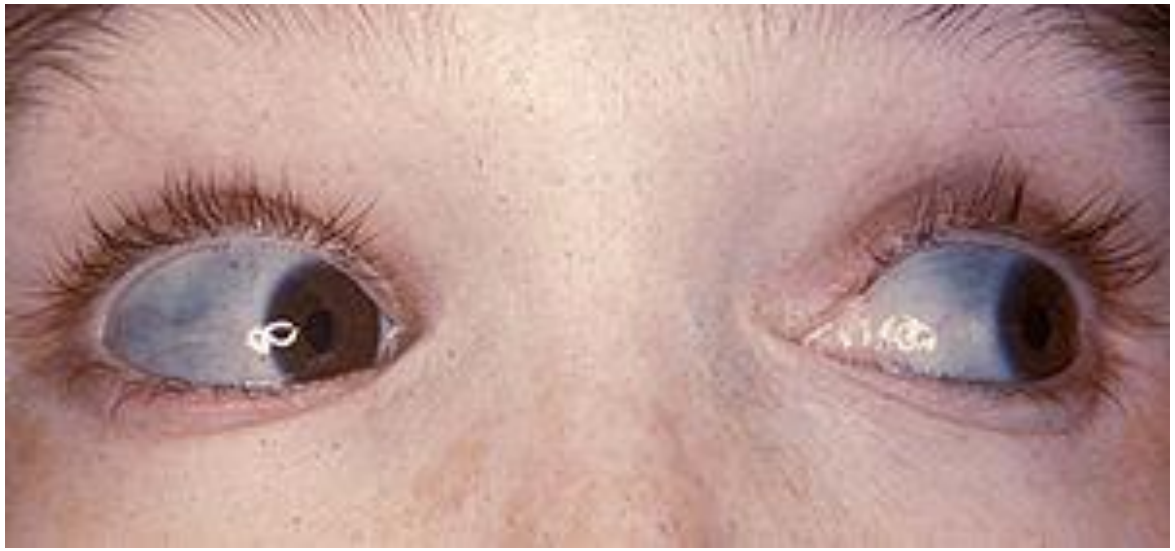
Osteogenesis Imperfecta

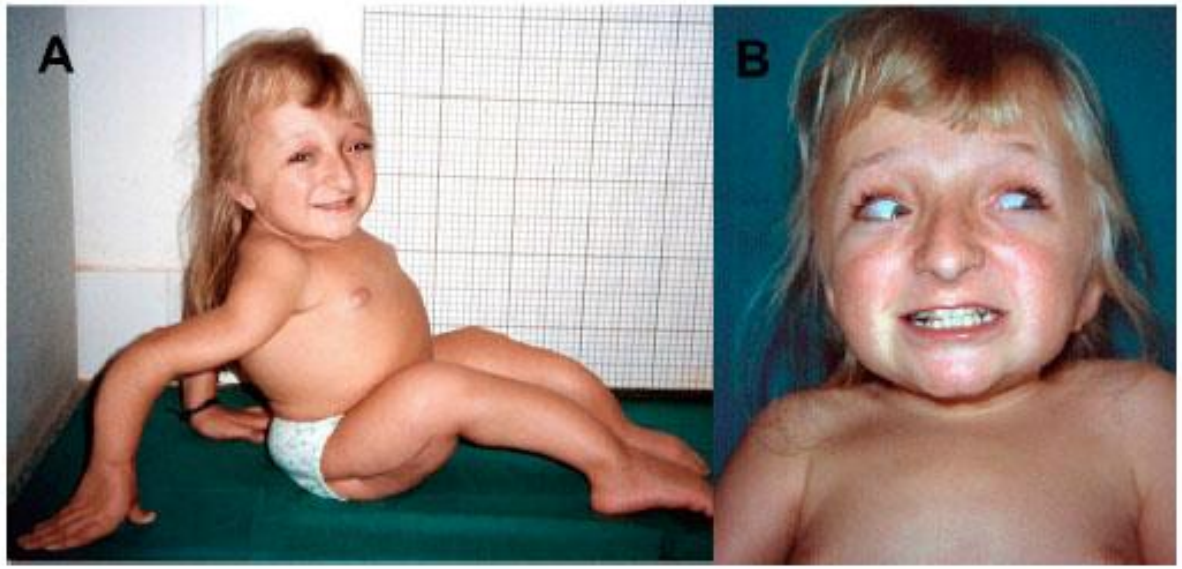
Healthy Bone



Brittle Bone

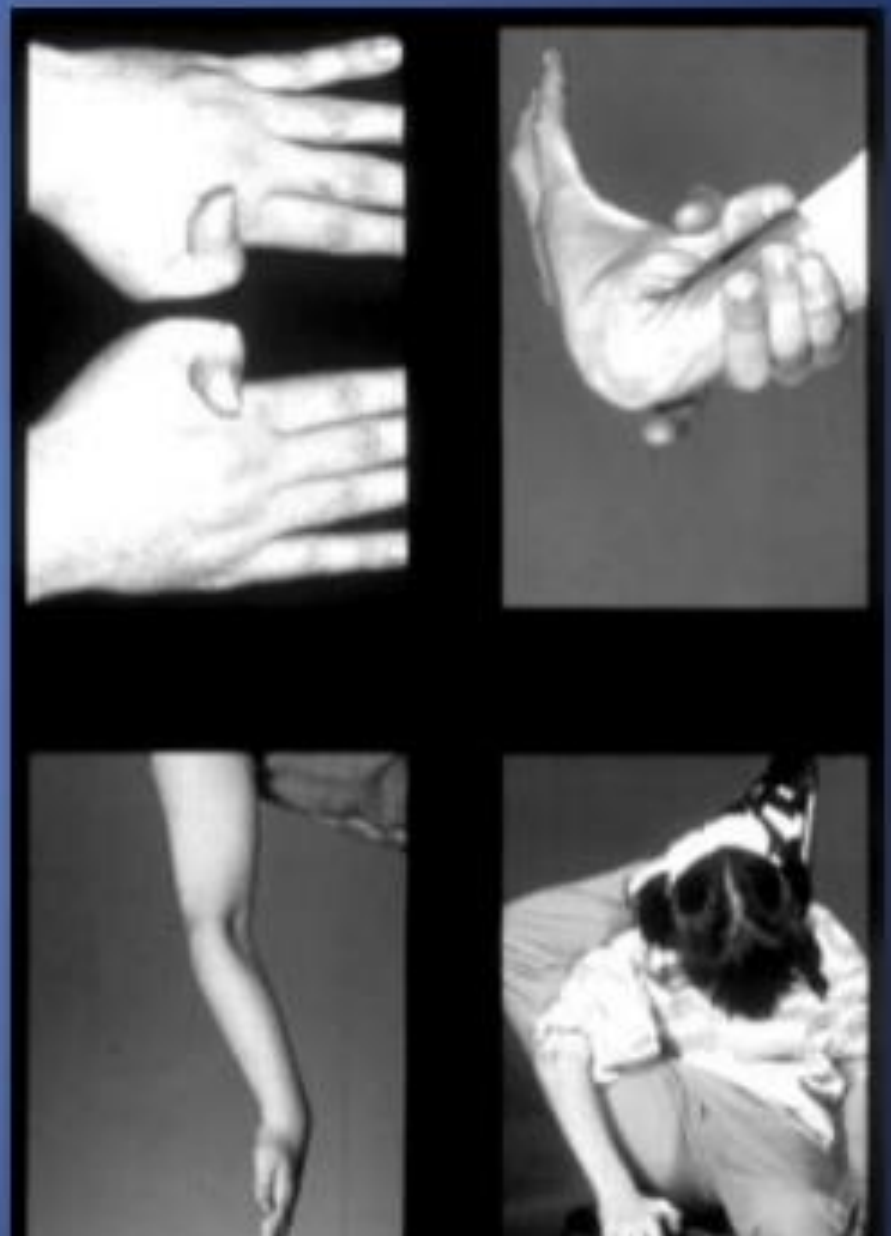






2. Chondrodysplasias

- Chondrodysplasias are a mixed group of hereditary disorders affecting cartilage.
- One example is Stickler syndrome, manifested by degeneration of joint cartilage and of the vitreous body of the eye.
- **CAUSE**
  - Mutations in the *COL2A1* gene, leading to abnormal forms of type II collagen.
- **EFFECT**
  - shortlimbed dwarfism
  - skeletal deformities.



3. Ehlers Danlos Syndrome

History

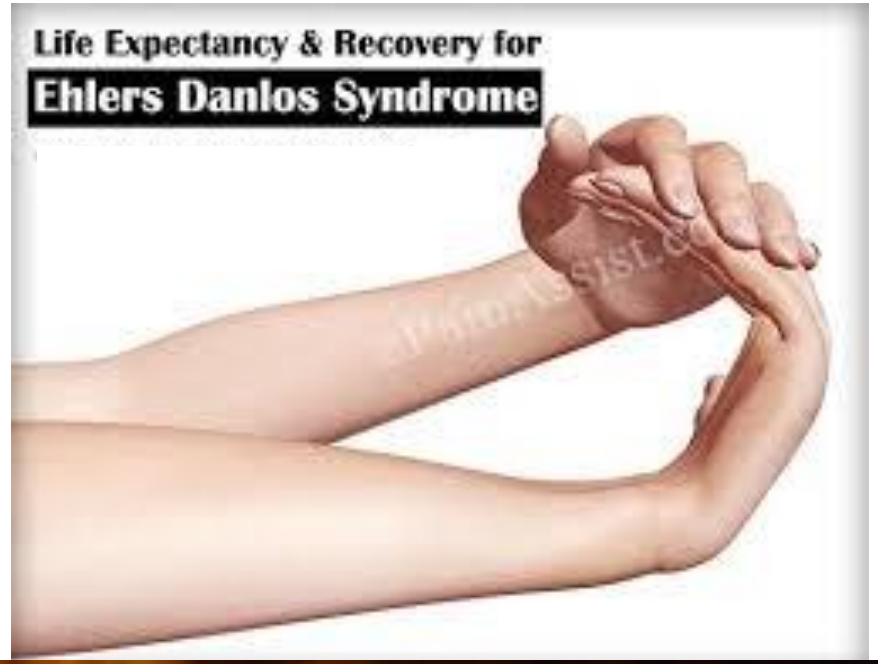
- It was first discovered in 400 BC by Hipprocrates. It gets its name from two European dermatologists, Edvard Ehlers and Henri-Alexandre Danlos. It is known to be one of the earliest causes for bruising and bleeding.

كدمات

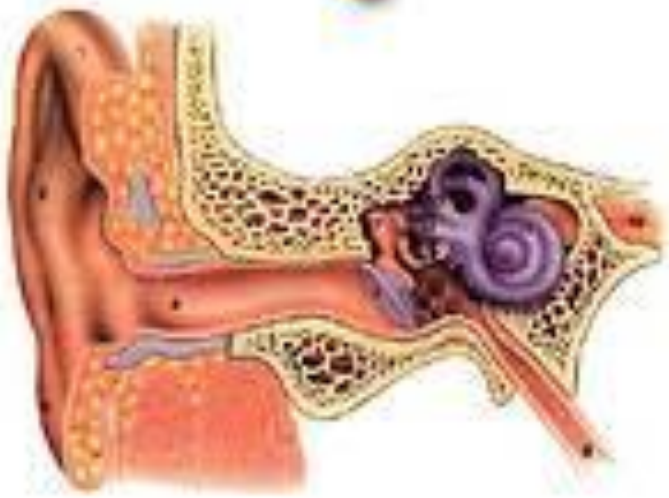
- Mutations in at least 19 genes have been found to cause the Ehlers-Danlos syndromes.

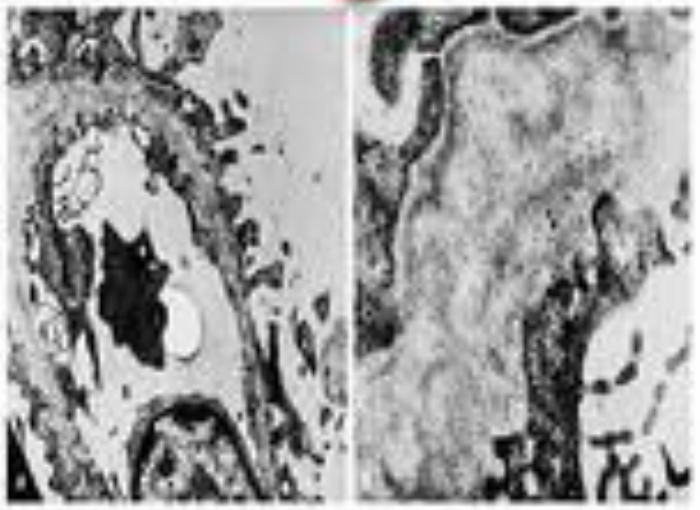
- Many people with the Ehlers-Danlos syndromes have soft, velvety skin that is highly stretchy (elastic) and fragile. Affected individuals tend to bruise easily, and some types of the condition also cause abnormal scarring.

- Some forms of Ehlers-Danlos syndrome can cause unpredictable tearing (rupture) of blood vessels, leading to internal bleeding and other potentially life-threatening complications.


Life Expectancy & Recovery for
Ehlers Danlos Syndrome

4. Alport syndrome

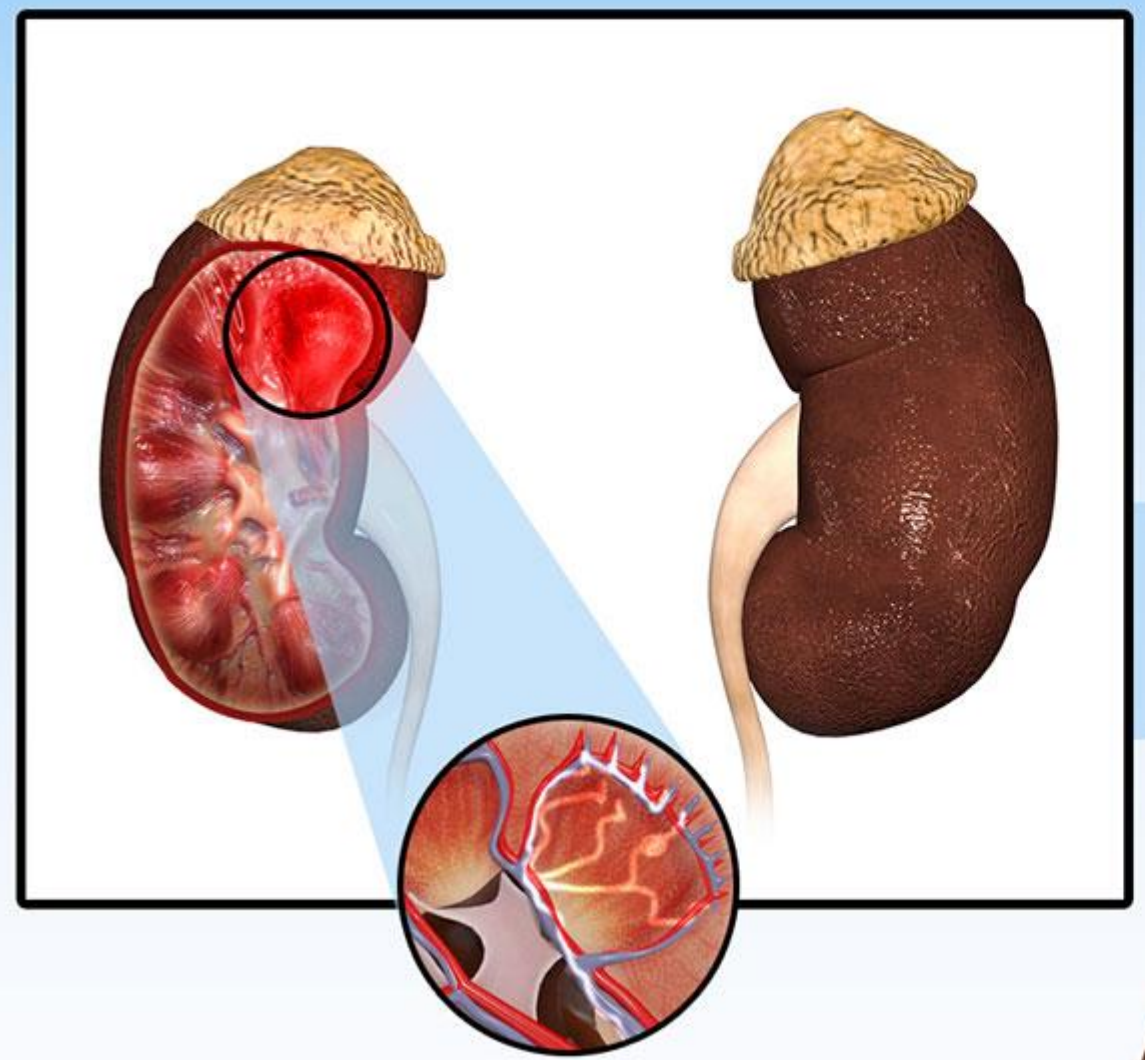




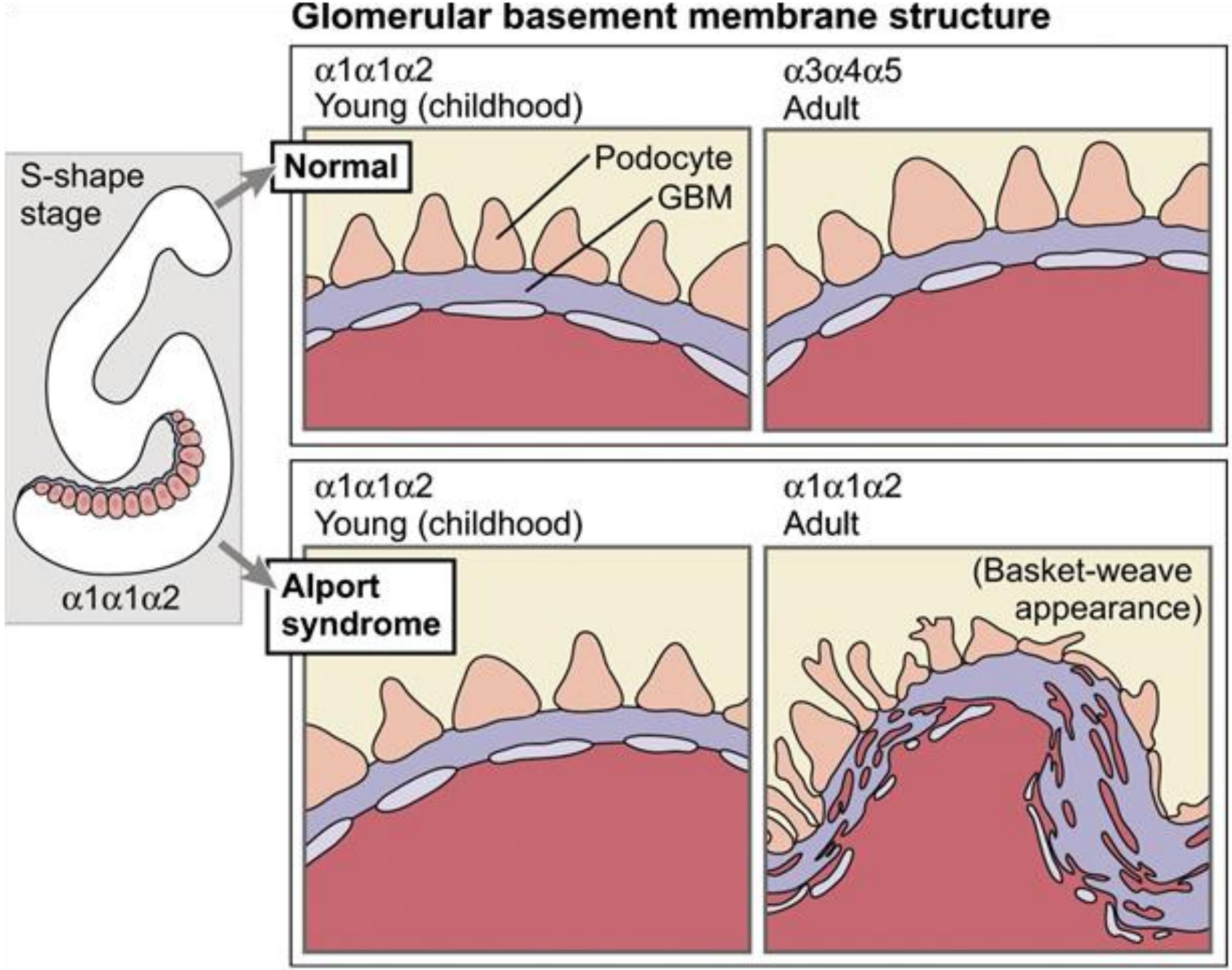
Inherited in an X-linked, mutations in the COL4A5 gene , loss of type IV collagen.
Progressive loss of kidney function and hearing.
Alport syndrome can also affect the eyes.
The presence of blood in the urine (hematuria) is almost always found

Hereditary Nephritis or Alport Syndrome

Kidney Abnormality - Glomerulonephritis

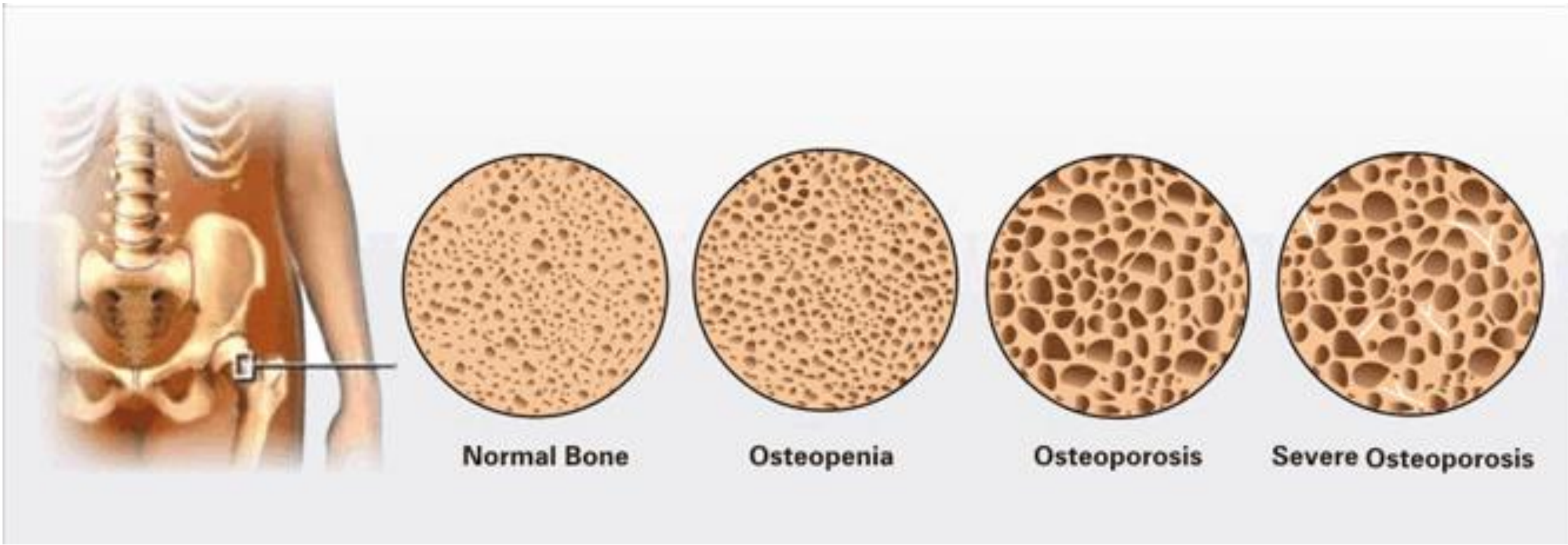


Alport Syndrome is a Group of Symptoms: Glomerulonephritis, Deafness and Visual Abnormalities


Glomerular basement membrane structure
S-shape stage
α1α1α2
Normal
α1α1α2
Young (childhood)
α3α4α5
Adult
Podocyte
GBM
Alport syndrome
α1α1α2
Young (childhood)
α1α1α2
Adult
(Basket-weave appearance)

5. Osteoporosis

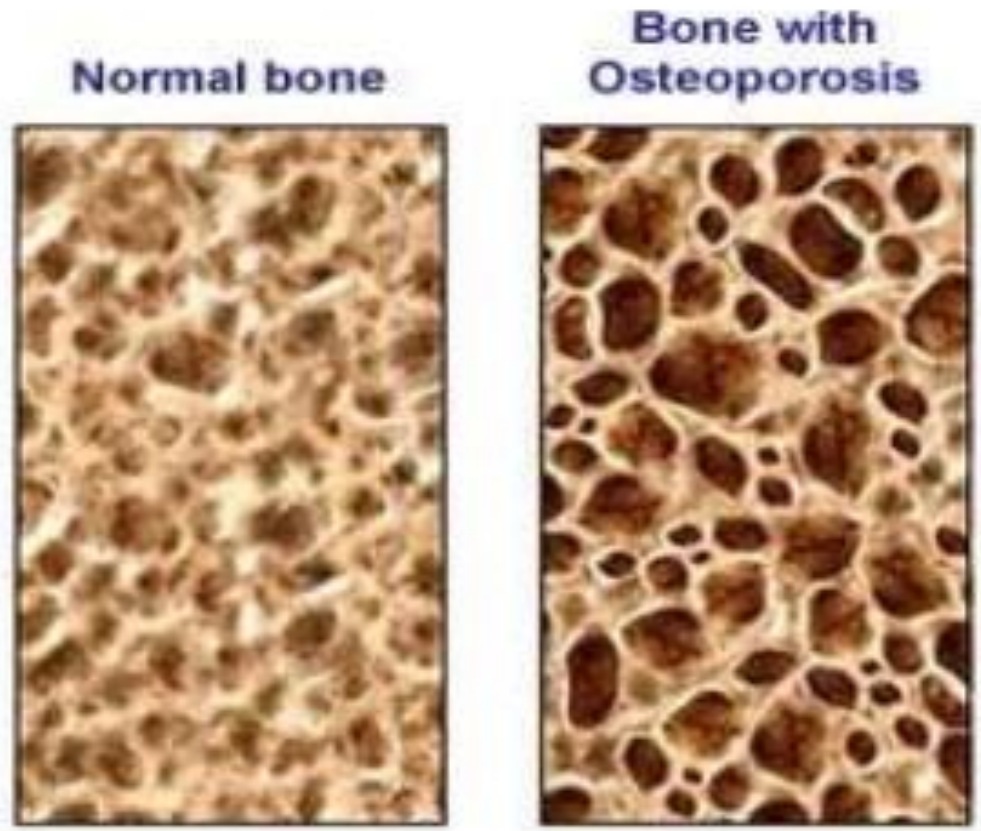
- By aging bones become thin with decreased strength.
- Osteoporosis is a disease in which bones become very weak and more likely to break.
- It often develops unnoticed over many years, with no symptoms or discomfort until a bone breaks.
- Osteoporosis is associated with reduced levels of collagen in the skin and bones.


Normal Bone
Osteopenia
Osteoporosis
Severe Osteoporosis

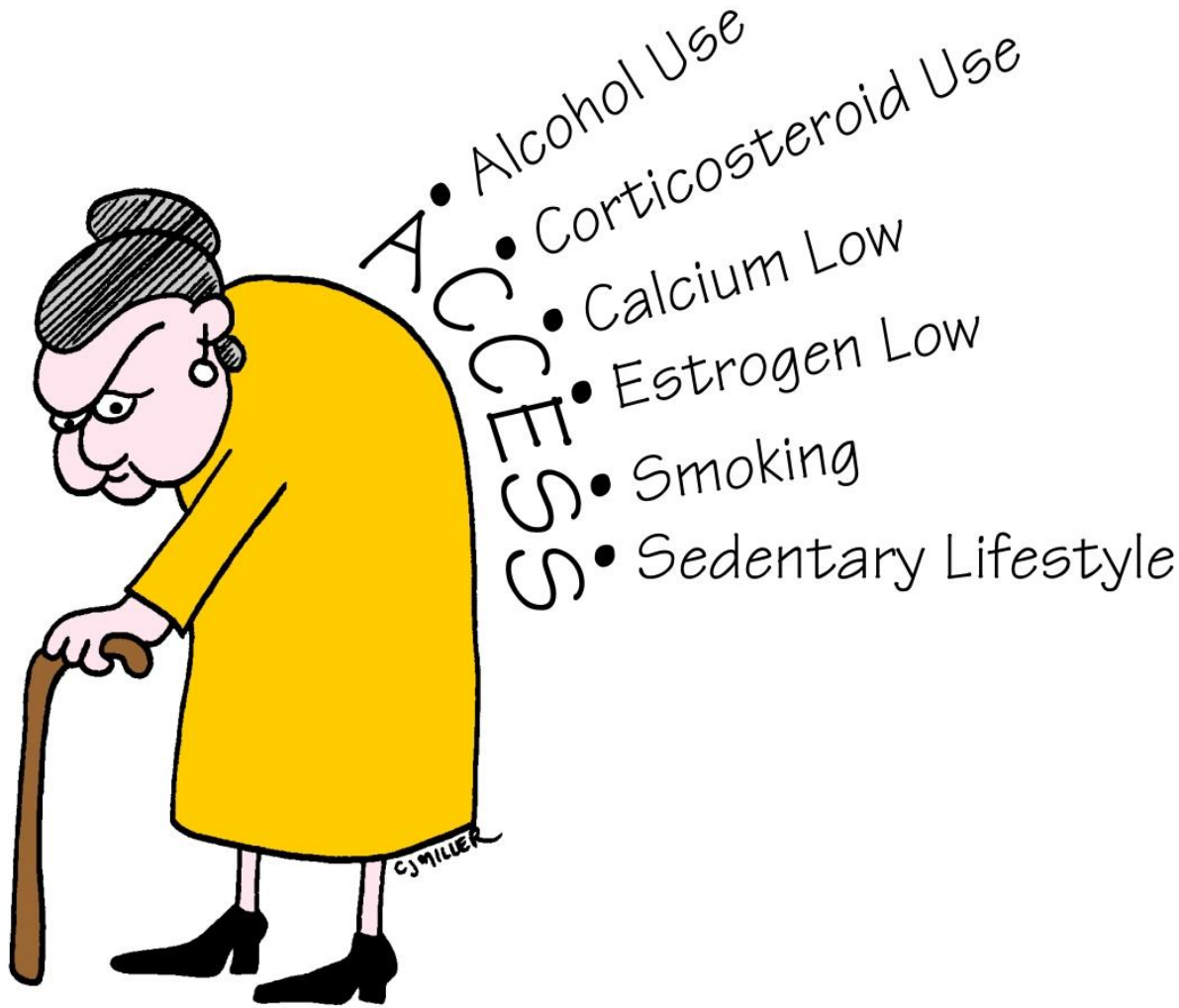
Osteoporosis

WHO definiton Osteoporosis (2003)

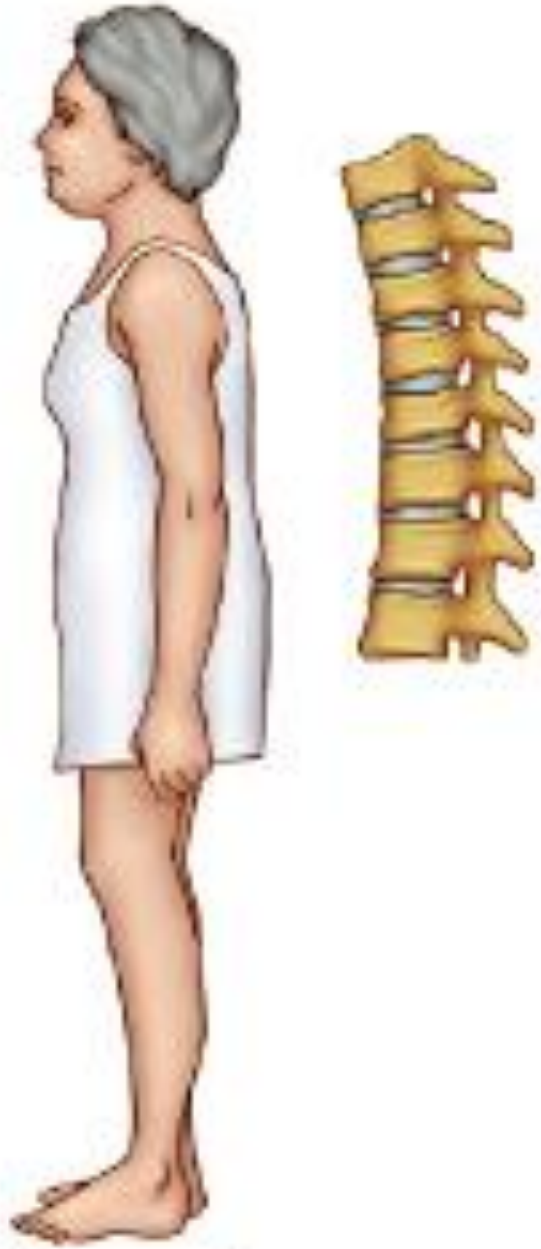
- Disease characterised by:
  - low bone mass
  - microarchitectural deterioration
  - enhanced bone fragility
  - increase in fracture risk



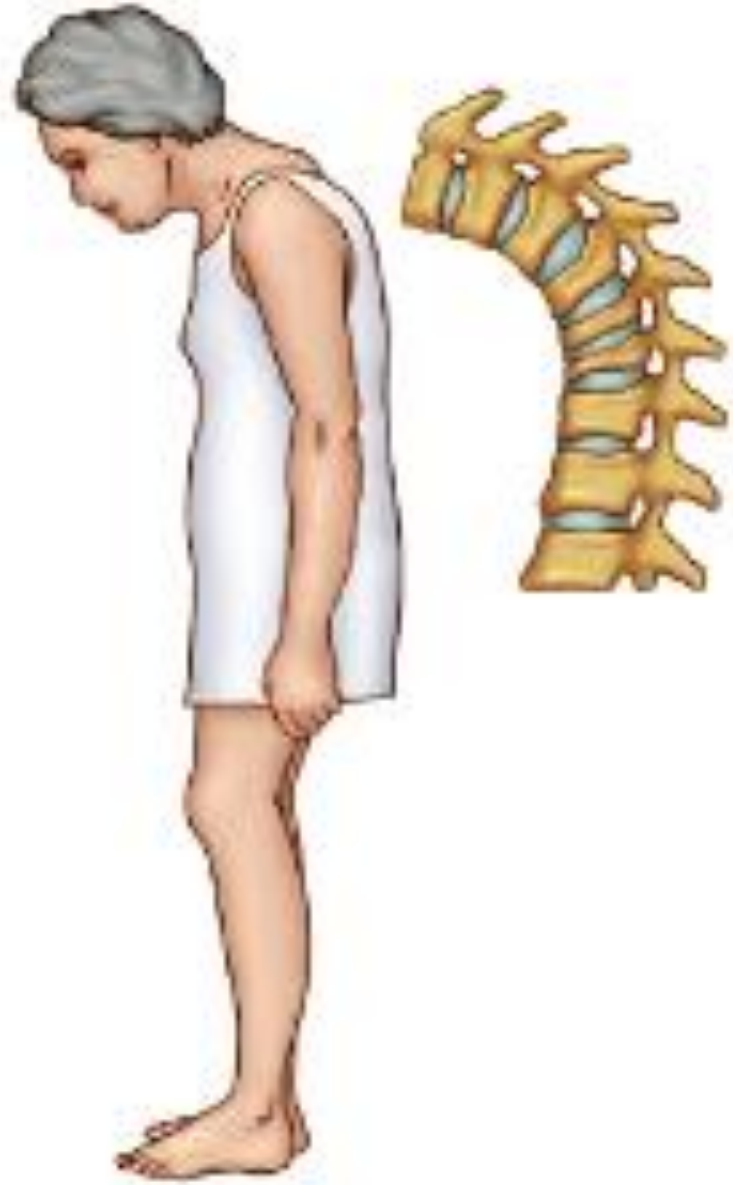
OSTEOPOROSIS RISK FACTORS



"Access" (leads to) Osteoporosis

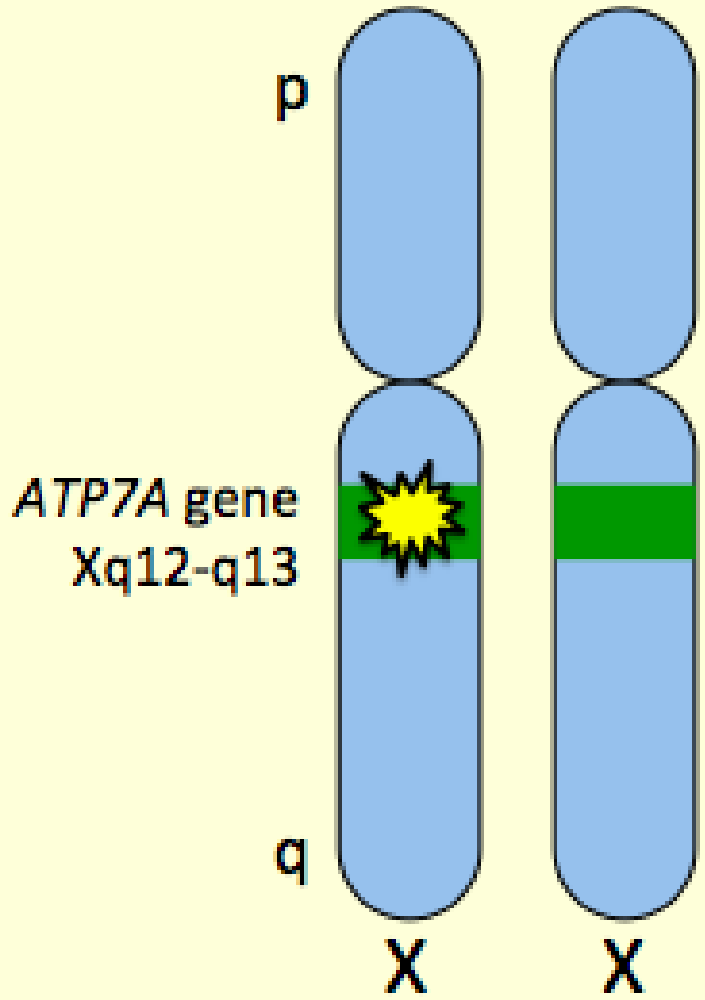


Normal

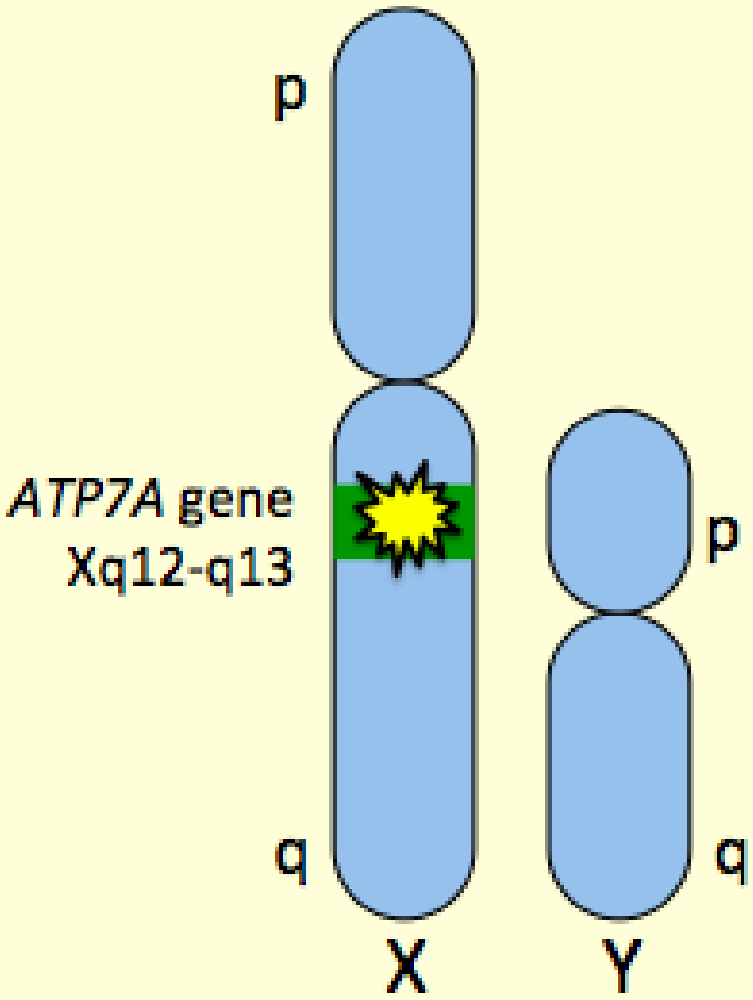


Osteoporosis

6. Menkes disease



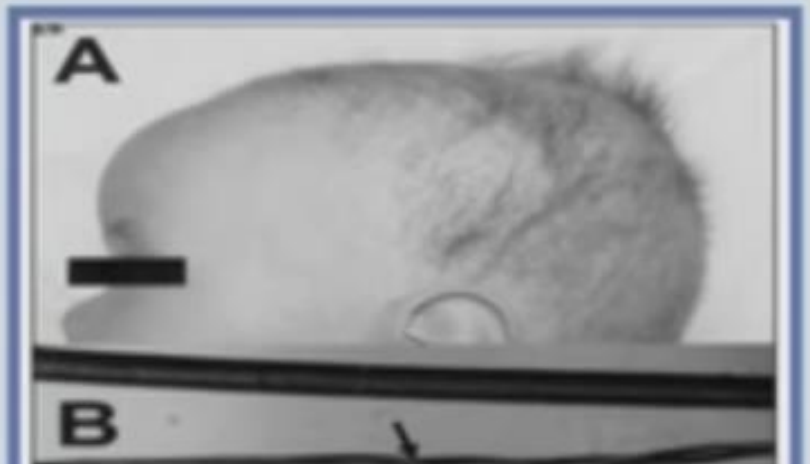
Female carrier



Affected male

6. Menkes Disease

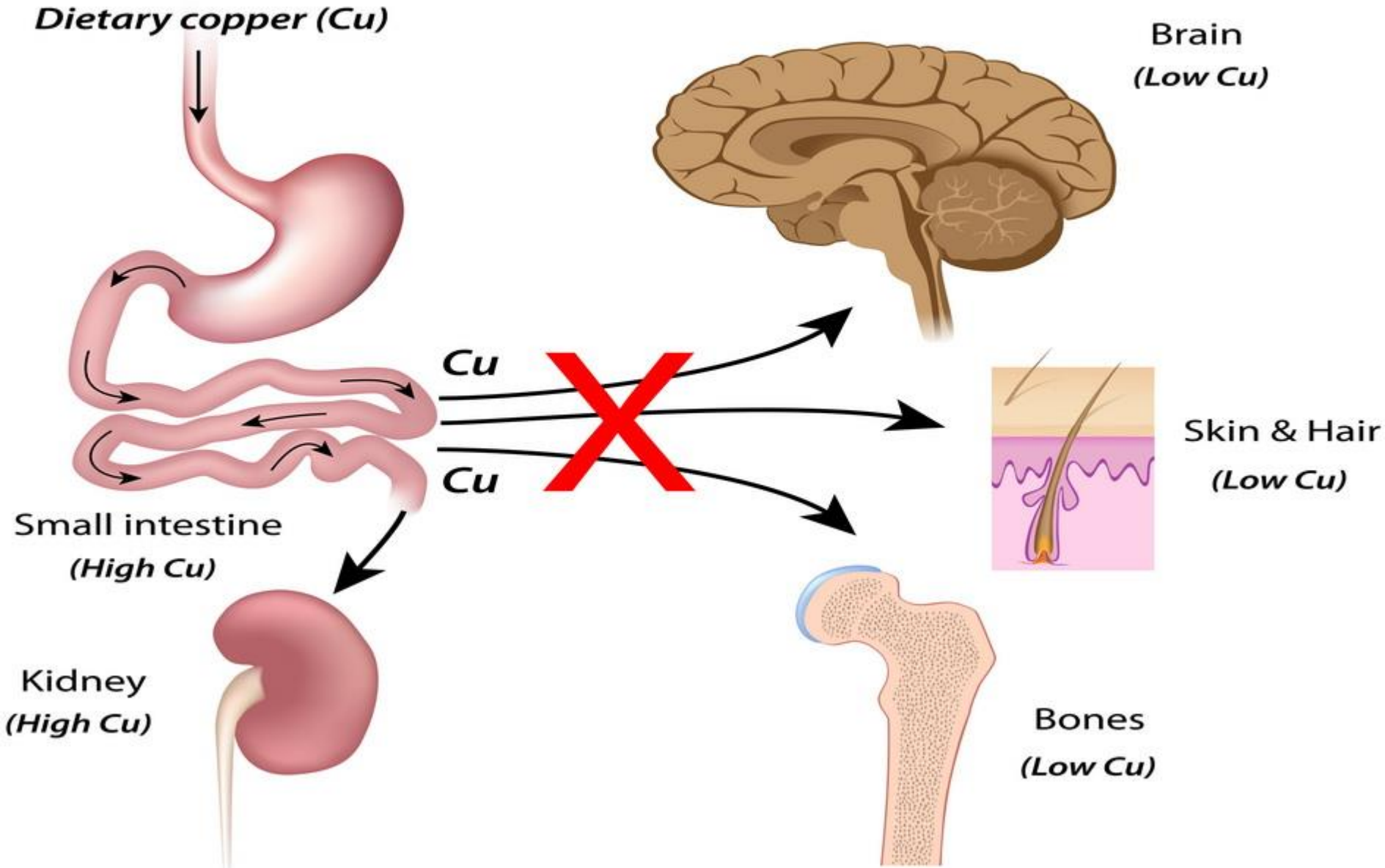
- ✓ Other names: Menkes syndrome, copper transport disease, steely hair disease, kinky hair disease, or Menkes kinky hair syndrome
- ✓ X linked defect in copper binding P type ATPase (ATP7A mutation) in intestinal cells
- ✓ Low serum Cu levels with deposition of Cu in intestinal cells
- ✓ Decreased activity of Cu dependent lysyl oxidase leads to defective collagen cross-linking
- ✓ Characterized by sparse and coarse brittle hair, growth failure, and deterioration of the nervous system



6. Menkes disease

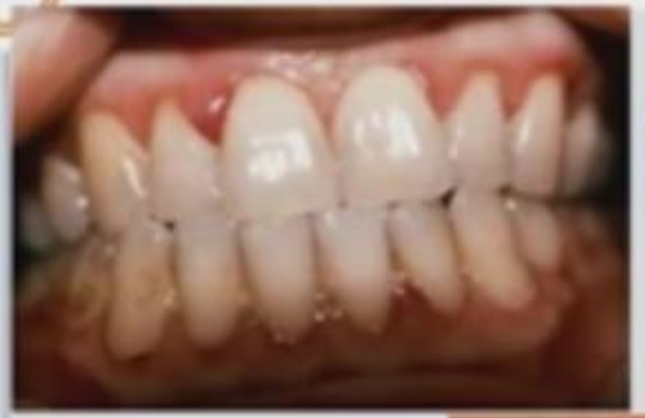
- Menkes disease is a neurodegenerative disease.
- Copper storage proteins in brain (Cerebrocuprein) and liver (Hepatocuprein) are abnormally low whereas they are relatively high in the intestinal mucosa and the kidneys.
- The defective gene responsible for Menkes disease is responsible for the synthesis of proteins which regulate copper levels in the body.

Menkes Disease



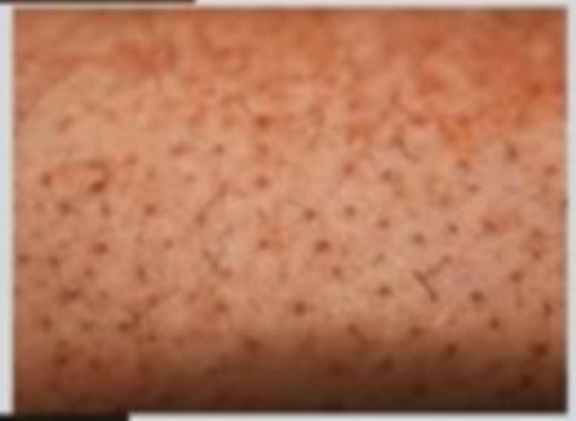
7. Scurvy

- Scurvy is a disease resulting from a deficiency of ascorbic acid
- Ascorbic acid is required as coenzyme for prolyl hydroxylase and lysyl hydroxylase in collagen formation
- Symptoms and signs include: skin changes with roughness, easy bruising and petechiae, gum bleeding, loosening of teeth, poor wound healing



Gingival hemorrhage

Corkscrew hair



Periungual hemorrhage


THANK YOU!